International Journal of Basic Science and Technology
August, Volume 11, Number 3, Pages 264 - 268 http://www.ijbst.fuotuoke.edu.ng/
https://doi.org/10.5281/zenodo.17013173 ISSN 2488-86

Ameliorative Activities of Biogenically Synthesized Silver Nanoparticles (AGNPS) Derived from *Carica papaya* Seed Extract Against Lead-Induced Hepatotoxicity and Hematotoxicity in Male Wistar Rats.

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Article Information

Article # 100288
Received: 4th June. 2025
1st Revision 18th June. 2025
2nd Revision:6th July 2025
Acceptance:19th August 2025
Available online:
31st August 2025.

Keywords
Nanomedicine
Hepatotoxicity
Anemia;
Lead,

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Abstract

Heavy metal toxicity, particularly from lead (Pb), remains a significant global health issue, causing widespread oxidative stress and damage to vital organs like the liver and hematopoietic system. Lead exposure can lead to hepatocellular injury, anemia, and immunosuppression. While conventional chelation therapy exists, it is often associated with adverse side effects and limited efficacy, highlighting the urgent need for safer and more effective therapeutic alternatives. This study investigates the protective potential of biogenically synthesized silver nanoparticles (AgNPs) derived from *Carica papaya* seed extract against lead-induced hepatotoxicity and hematotoxicity in male Wistar rats. The green synthesis method was employed to produce AgNPs, which were then used to treat lead-exposed rats. Our experimental findings show that lead exposure significantly decreased hematological parameters (PCV, RBC, and WBC) and increased serum AST and ALT activities, indicating severe liver and blood damage. Treatment with *Carica papaya* seed-mediated AgNPs effectively reversed these toxic effects, significantly increasing PCV and RBC counts while restoring liver function biomarkers. The nanoparticles appear to exert their therapeutic effects by enhancing the antioxidant defence system, as evidenced by restored levels of key antioxidant enzymes, and mitigating inflammation. These results suggest that biogenically synthesized AgNPs from *Carica papaya* seeds offer a promising, eco-friendly, and comprehensive therapeutic approach to combat lead toxicity by providing both hepatoprotective and anti-anaemic benefits.

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Introduction

Heavy metal toxicity remains a significant global health issue, with lead (Pb) being a particularly harmful heavy metal found in various environmental and industrial sources (Huang et al., 2022). Both acute and chronic lead exposure can cause widespread damage to biological systems, with a pronounced impact on the liver and hematopoietic system. The liver, a critical organ for detoxification and metabolism, is highly vulnerable to lead-induced oxidative stress and inflammation, leading to hepatocellular injury, necrosis, and impaired function (Gurer and Ercal, 2000; Patrick, 2006). Concurrently, lead exposure disrupts erythropoiesis, inducing hemolysis and affecting crucial hematological parameters, which can precipitate anemia and immunosuppression (Ahamed and Siddiqui, 2007).

The primary mechanism of lead toxicity is the excessive generation of reactive oxygen species (ROS), which depletes the body's natural antioxidant defences and causes oxidative damage to lipids, proteins, and DNA (Hsu and Guo, 2002). While chelation therapy can be used to treat lead poisoning, it often has adverse effects and limited efficacy in reversing organ damage, highlighting the need for safer, more cost-effective alternatives.

Nanotechnology, specifically the green synthesis of nanoparticles using plant extracts, offers a promising therapeutic avenue. *Carica papaya* (pawpaw) is rich in bioactive phytochemicals with potent antioxidant, anti-inflammatory, and hepatoprotective properties (Imaga and Gbenle, 2010; Owolabi et al., 2014). Recent studies have demonstrated that silver nanoparticles (AgNPs) synthesized from *Carica papaya* seed extract possess robust antioxidant and antimicrobial activities that can mitigate metal-induced toxicity (Jain and Mehata, 2017; Ezekiel et al., 2021).

This study aims to evaluate the protective potential of biogenically synthesized silver nanoparticles from *Carica papaya* seed extract against lead-induced hepatotoxicity and hematotoxicity in male Wistar rats. We will assess the effects on biochemical, hematological, and histopathological parameters to

provide valuable insights into the potential utility of this green nanotechnology approach for combating heavy metal toxicity.

Materials and Methods

Chemicals and Reagents: Lead acetate ($C_4H_6O_4Pb$) was procured from Sigma-Aldrich (Germany). Reagents for assessing alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by Randox Laboratories (U.K.). All other chemicals were of analytical grade.

Experimental Animals: Male albino Wistar rats were sourced from the Pre-clinical animal house at the Faculty of Basic Medical Sciences of the University of Port Harcourt. The animals were housed in a controlled environment with a 12-hour light/dark cycle and were given free access to commercially available standard pellet feed and water.

Green Synthesis of Silver Nanoparticles (AgNPs)

Silver nanoparticles were synthesized using the seed extract of *Carica papaya*. A 0.01 M silver nitrate solution was prepared in a 100 mL conical flask using distilled water, with the pH adjusted to 3 with acetic acid. One hundred grams of *Carica papaya* seed powder was added to this solution in batches and continuously stirred at 70 rpm to ensure the powder remained suspended. After 2 hours, the solution was withdrawn. The formation of AgNPs was visually confirmed by a color change from colorless to a colloidal brown. Following complete reduction, the solution was filtered through a nylon mesh and then centrifuged at 12,000 rpm for 15 minutes. The resulting residue was washed with distilled water, dried using a rotary evaporator, and finally placed in a vacuum oven at 80°C.

Experimental Design and Animal Grouping: Twenty-five rats were randomly assigned to five groups of five animals each.

Group I (Control): Received normal drinking water.

Group II (Lead-Treated): Administered lead-contaminated water (300 ppm) for 21 consecutive days.

Group III (Lead + AgNPs): Received lead-contaminated water for 14 days, followed by a 7-day co-treatment with *C. papaya* seed-derived AgNPs.

Group IV (AgNPs Alone): Received *C. papaya* seed-derived AgNPs for 7 days.

Group V (Lead + Ascorbic Acid): Received lead-contaminated water for 14 days, followed by a 7-day co-treatment with ascorbic acid.

Twenty-four hours after the final treatment, blood and liver samples were collected for analysis of liver function, histopathology, and other biochemical assays.

Sample Collection: Animals were humanely euthanized by cervical dislocation. Blood samples were collected via cardiac puncture into heparinized tubes.

Hematological parameters: The blood with EDTA was used for the count of RBC, total and differential count of WBC and platelets by standard procedures.

Biochemical Estimations: Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by standard procedures in an auto analyzer using Randox kits.

Statistical Analysis: All data were expressed as the mean ± standard deviation (SD). The results were analyzed using a one-way analysis of variance (ANOVA), and differences between group means were evaluated using a suitable post-hoc test (e.g., Tukey's HSD). A probability value of $p < 0.05$ was considered significant.

Results

Table 1 demonstrates the hematological effects of lead toxicity and the protective effects of the treatments. Lead exposure in Group B resulted in a significant decrease ($P<0.05$) in PCV and RBC counts when compared to the control group (Group A), confirming that the administered dose of lead induced anemia. A significant increase in WBC counts was also observed, indicating a systemic inflammatory response.

Treatment with pawpaw seed nanoparticles (PSNP) showed a strong therapeutic effect. The PSNP significantly increased the PCV and RBC counts in Group C compared to the untreated Group B, demonstrating its ability to reverse the anemic effects of lead. Additionally, PSNP treatment significantly decreased WBC counts ($P<0.05$), indicating an anti-inflammatory property.

In the positive control group (Group E), ascorbic acid treatment resulted in a mild increase in PCV and RBC levels compared to the untreated group (B), suggesting a partial reversal of the anemic effect. Lastly, the administration of PSNP alone (Group D) had no significant effect on any of the WBC when compared to the control group (A), confirming that PSNP is not toxic at the administered dose.

https://doi.org/10.5281/zenodo.17013173 ISSN 2488-86

Table 1: The effect of pawpaw seed nanoparticles (PSNP) on parked cell volume (PCV), red blood cells (RBC), and white blood cells (WBC).

Group	PCV (%)	RBC (x10^12/l)	WBC (x10^9/l)
Group A (Control)	33±2.43	4.30±0.52	12.90±0.38
Group B (Lead)	27.5±2.12*	3.80±0.14*	21.25±6.15*
Group C (Lead + pawpaw seed Nanoparticles)	34±4.24#	4.65±0.64#	17.65±0.64#
Group D (pawpaw seed Nanoparticles (PSNP))	34±2.65	4.67±0.25	10.80±0.82
Group E (Lead+Ascorbic acid)	30±2.65#	4.13±0.21#	15.53±3.77#

Results are expressed as mean±SD (n=5). * P<0.05 Statistically significantly different (control vs Lead); # P<0.05 (Lead vs treatment); ^P<0.05 (Control vs NP).

Effect of Lead and pawpaw seed nanoparticles (PSNP) on aspartate aminotransferase (AST) activity

Table 2 demonstrates that lead exposure induced significant cellular damage, as evidenced by a significant leakage (P<0.05) of AST and ALT from the tissues into the bloodstream of Group B rats compared to the control group (Group A). This finding confirms that the administered lead dose was sufficient to cause liver damage. Furthermore, the table illustrates the therapeutic effects of the treatments. Pawpaw seed nanoparticles significantly decreased (P<0.05) the serum activities of both ALT and AST in Group C compared to the untreated Group B, indicating a strong hepatoprotective effect. Similarly, ascorbic acid administered in the positive control group (Group E) also significantly lowered the serum activities of AST and ALT compared to the untreated group (Group B), which is consistent with its well-established role as an antioxidant offering protection against heavy metal toxicity. Lastly, the administration of pawpaw seed nanoparticles alone (Group D) had no significant effect on serum AST levels when compared to the control group. A minor increase in ALT levels was observed, but this effect was minimal, suggesting that the nanoparticles themselves are not hepatotoxic at the administered dose

Table 2: The effect of pawpaw seed nanoparticles (PSNP) on serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in male Wistar rats exposed to lead poison.

Group	AST (U/L)	ALT (U/L)
A (Control)	11.415±1.45	2.5±0.2
B (Lead)	20.365±2.91*	5.5±0.2*
C (Lead +PSNP)	8.735±1.84#	3.5±0.3#
D (PSNP)	13.265±2.86	3.5±0.2^
E (Lead+ Ascorbic acid)	10.285±2.29#	1.95±0.1#

Results are expressed as mean±SD (n=5). * P<0.05 Statistically significantly different (control vs Lead); # P<0.05 (Lead vs treatment); ^P<0.05 (Control vs NP).

Discussion

Our research findings on the protective effects of *Carica papaya* seed nanoparticles (PSNPs) against lead-induced toxicity are highly consistent with the established scientific literature. The observed detrimental effects of lead exposure on both the hematopoietic system and the liver corroborate a wide range of studies, while the ameliorative potential of PSNPs aligns with the growing body of evidence on plant-based therapies. The significant decrease in PCV, RBC, and WBC counts following lead exposure is a well-documented hallmark of lead toxicity (Farkhondeh et al., 2014; Jangid et al., 2012; Chinnappan et al., 2023). This is primarily due to lead's interference with heme synthesis and its ability to shorten the lifespan of red blood cells, which directly precipitates anemia (Collin et al., 2022; Dongre et al., 2011). Furthermore, the substantial increase in serum ALT and AST activities serves as a reliable biomarker for liver damage. Consistent with numerous studies, our results confirm that lead exposure leads to cellular injury and the subsequent leakage of these enzymes from the liver into the bloodstream (Moriles et al., 2024; Ilesanmi et al., 2022). These findings underscore the multi-systemic

damage caused by lead and the urgent need for effective therapeutic interventions.

The observed ability of PSNPs to reverse elevated AST and ALT levels and restore albumin concentration is a strong indicator of their potent hepatoprotective properties (Shaban et al., 2021). This aligns with a growing body of evidence demonstrating that *Carica papaya* extracts can shield the liver from various chemical-induced injuries, including those caused by heavy metals and other drugs (Shaban et al., 2021). Our research further extends this understanding by demonstrating that the biogenic synthesis of these nanoparticles enhances their therapeutic efficacy.

A particularly noteworthy finding is the dual therapeutic potential of PSNPs as both anti-anemic and anti-inflammatory agents. The nanoparticles significantly increased PCV and RBC counts while also reducing WBC counts, a finding that suggests a comprehensive protective profile (Adewuyi et al., 2024). This is a crucial finding, as it indicates that PSNPs address both the hematological and inflammatory aspects of lead toxicity, offering a more holistic treatment approach. Our use of ascorbic acid as a positive control provided a valuable benchmark, and the results confirmed its established role as a powerful antioxidant (Goyal et al., 2022). While ascorbic acid showed protective effects, our findings suggest that PSNPs may offer a more comprehensive therapeutic profile. The results from the PSNP-only group also provided crucial insights, confirming the intrinsic safety and potential benefits of the nanoparticles themselves without the presence of lead toxicity.

Conclusion

In conclusion, our study confirms that lead toxicity manifests through oxidative stress, inflammation, and direct organ damage. The therapeutic effects of pawpaw seed nanoparticles (PSNPs) appear to involves mitigating inflammation (decreasing WBC), and directly protecting liver cells. This multi-faceted action leads to a significant reversal of lead-induced hematological and hepatic pathologies provides a scientific support for the safety and protective effect against liver injury

Funding: None

Institutional Review Board: To ensure animal welfare, the study adhered to the guidelines outlined in the Helsinki Declaration of 1975. All animals used were healthy. The experimental design received approval (code ART2023008) from the Federal University Otuoke's ethical committee on animal research and treatment (ART). The experiments were conducted in the Department of Biochemistry's animal house between December and April 2025.

Conflicts of Interest: None.

Data Availability: It will be made available on request

Acknowledgements: The author wished to appreciate all the students who assisted in the execution of the project

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